Amendments to the Specification:

Please delete the "cross-reference to related applications" section.

~~This application is a continuation in part of USSN 322,289, filed May 28, 1999, which is incorporated by reference in its entirety for all purposes.~~

Please replace the paragraph beginning on page 2, line 21 of the specification with the following replacement paragraph.

~~This application is related to Townsend and Townsend and Crew Attorney Docket 015270-004750PC, filed May 26, 2000, PCT/US98/25386, filed November 30, 1998, USSN 60/067,740, filed December 2, 1997, USSN 60/080,970, filed April 7, 1998, and USSN 09/201,430, filed November 30, 1998, each of which is incorporated by reference in its entirety for all purposes.~~

This application is related to International Application No. PCT/US00/14810 filed May 26, 2000, Publication No. WO 00/72880; U.S. Application No. 322,289, filed May 28 1999; PCT/US98/25386, filed November 30, 1998, Publication No. WO 99/27944; U.S. Application No. 09/201,430, filed November 30, 1998; U.S. Application 60/067,740, filed December 2, 1997; and, U.S. Application No., filed April 7, 1998; each of which is incorporated by reference in its entirety for all purposes.

Please replace the paragraph beginning on page 7, line 14 of the specification with the following replacement paragraph.

Fig. 10: Lymphocyte Proliferation Assay on spleen cells from AN1792-treated (Fig. 10A)~~(upper panel)~~ or PBS-treated (Fig. 10B) ~~(lower panel)~~.

Please replace the paragraph on page 7, beginning on line 27 with the following replacement paragraph.

Figs. 15~~(A-E)~~A-E: Aβ levels in the cortex of 12-month old PDAPP mice treated with AN1792 or AN1528 in combination with different adjuvants. The Aβ level for individual mice in each treatment group, and the median, mean, and p values for each treatment group are shown.

After the paragraph beginning on page 7, line 27, please add the following five new paragraphs.

Fig. 15A: The values for mice in the PBS-treated control group and the untreated control group.

Fig. 15B: The values for mice in the AN1528/alum and AN1528/MPL-treatment groups.

Fig. 15C: The values for mice in the AN1528/QS21 and AN1792/Freund's adjuvant treatment groups.

Fig. 15D: The values for mice in the AN1792/Thimerosol and AN1792/alum treatment groups.

Fig. 15E: The values for mice in the AN1792/MPL and AN1792/QS21 treatment groups.

Please replace the paragraph beginning on page 7, line 32 with the following replacement paragraph:

Fig. 19: Epitope Map: Restricted N–terminal Response. Day 175 serum from cynomolgus monkeys was tested by ELISA against a series of 10–mer overlapping peptides (SEQ ID NOS:1-41) covering the complete AN1792 sequence. ~~The results for peptide VGSNKGAII (SEQ ID NO:32) are shown twice.~~ Animal number F10920M shows a representative N–terminal restricted response to the peptide DAEFRHDSGY (SEQ ID NO:9) which covers amino acids 1–10 of the AN1792 peptide which was used as immunizing antigen.

Please replace the paragraph beginning at page 8, line 5 with the following replacement paragraph:

Fig. 20: Epitope Map: Non–restricted N–terminal response. Day 175 serum from cynomolgus monkeys was tested by ELISA against a series of 10-mer overlapping peptides (SEQ ID NOS:1-41) covering the complete AN1792 sequence. ~~The results for peptide VGSNKGAII (SEQ ID NO:32) are shown twice.~~ Animal number F10975F shows a representative non–restricted N–terminal response. Reactivity is seen against the two peptides N–terminal and one peptide C-terminal to the peptide DAEFRHDSGY (SEQ ID NO:9) which covers amino acids 1–10 of the AN1792 peptide.

Please replace the paragraph beginning at page 16, line 16, with the following replacement paragraph:

In a further variation, an immunogenic peptide, such as a fragment of Aβ, can be presented by a virus or a bacteria as part of an immunogenic composition. A nucleic acid encoding the immunogenic peptide is incorporated into a genome or episome of the virus or bacteria. Optionally, the nucleic acid is incorporated in such a manner that the immunogenic peptide is expressed as a secreted protein or as a fusion protein with an outer surface protein of a virus or a transmembrane protein of a bacteria so that the peptide is displayed. Viruses or bacteria used in such methods should be nonpathogenic or attenuated. Suitable viruses include adenovirus, HSV, Venezuelan equine encephalitis virus and other alpha viruses, vesicular stomatitis virus, and other rhabdo viruses, vaccinia and fowl pox. Suitable bacteria include ~~Salmonella~~*Salmonella* and ~~Shigella~~*Shigella*. Fusion of an immunogenic peptide to HBsAg of HBV is particularly suitable. Therapeutic agents also include peptides and other compounds that do not necessarily have a significant amino acid sequence similarity with Aβ but nevertheless serve as mimetics of Aβ and induce a similar immune response. For example, any peptides and proteins forming β-pleated sheets can be screened for suitability. Anti-idiotypic antibodies against monoclonal antibodies to Aβ or other amyloidogenic peptides can also be used. Such anti-Id antibodies mimic the antigen and generate an immune response to it (*see Essential Immunology* (Roit ed., Blackwell Scientific Publications, Palo Alto, 6th ed.), p. 181). Agents other than Aβ peptides should induce an immunogenic response against one or more of the preferred segments of Aβ listed above (e.g., 1-10, 1-7, 1-3, and 3-7). Preferably, such agents induce an immunogenic response that is specifically directed to one of these segments without being directed to other segments of Aβ.

Please replace the paragraph beginning on page 46, line 21 with the following replacement paragraph:

The methods work by administering a reagent, such as antibody, that binds to Aβ in the patient~~to the patient~~, and then detecting the agent after it has bound. Preferred antibodies bind to Aβ deposits in a patient without binding to full length APP polypeptide. Antibodies binding to an epitope of Aβ within amino acids 1-10 are particularly preferred. In some methods, the antibody binds to an epitope within amino acids 7-10 of Aβ. Such antibodies typically bind without inducing a substantial clearing response. In other methods, the antibody binds to an epitope within amino acids 1-7 of Aβ. Such antibodies typically bind and induce a clearing response to Aβ. However, the clearing response can be avoided by using antibody fragments lacking a full length constant region, such as Fabs. In some methods, the same antibody can serve as both a treatment and diagnostic reagent. In general, antibodies binding to epitopes C-terminal of residue 10 ~~of Aβdo not~~of Aβ do not show as strong signal as antibodies binding to epitopes within residues 1-10, presumably because the C-terminal epitopes are inaccessible in amyloid deposits. Accordingly, such antibodies are less preferred.

Please replace the paragraph beginning at page 59, line 25, with the following replacement paragraph:

Spleens were removed from nine AN1792-immunized and 12 PBS-immunized 18-month old PDAPP mice 7 days after the ninth immunization. Splenocytes were isolated and cultured for 72 h in the presence of Aβ40, Aβ42, or Aβ40-1 (reverse order protein). The mitogen Con A served as a positive control. Optimum responses were obtained with >1.7 μM protein. Cells from all nine AN1792-treated animals proliferated in response to either Aβ1-40 or Aβ1-42 protein, with equal levels of incorporation for both proteins (Fig. 10A)~~(Fig. 10, Upper Panel)~~. There was no response to the Aβ40-1 reverse protein. Cells from control animals did not respond to any of the Aβ proteins (Fig. 10B)~~(Fig. 10, Lower Panel)~~.

Please replace the paragraph beginning at page 62, line 12, with the following replacement paragraph:

Preparation of the pBx6 protein: An expression plasmid encoding pBx6, a fusion protein consisting of the 100-amino acid bacteriophage MS-2 polymerase N-terminal leader sequence followed by amino acids 592-695 of APP (βAPP) was constructed as described by Oltersdorf et al., J. Biol. Chem. 265, 4492-4497 (1990). The plasmid was transfected into ~~E. coli~~*E. coli* and the protein was expressed after induction of the promoter. The bacteria were lysed in 8M urea and pBx6 was partially purified by preparative SDS PAGE. Fractions containing pBx6 were identified by Western blot using a rabbit anti-pBx6 polyclonal antibody, pooled, concentrated using an Amicon Centriprep tube and dialysed against PBS. The purity of the preparation, estimated by Coomassie Blue stained SDS PAGE, was approximately 5 to 10%.

Please replace the paragraph beginning on page 68, line 17 with the following replacement paragraph:

Groups of 7-9 month old PDAPP mice each are injected with 0.5 mg in PBS of polyclonal anti-Aβ or specific anti-Aβ monoclonals as shown below. The cell line designated RB44-10D5.19.21 producing the antibody 10D5 has the ATCC accession number PTA-5129, having been deposited on April 8, 2003. All antibody preparations are purified to have low endotoxin levels. Monoclonals can be prepared against a fragment by injecting the fragment or longer form of Aβ into a mouse, preparing hybridomas and screening the hybridomas for an antibody that specifically binds to a desired fragment of Aβ without binding to other nonoverlapping fragments of Aβ.

Please replace the paragraph beginning on page 76, line 17 with the following amended paragraph:

To prepare formulation doses with alum (Groups 1 and 5). Aβ peptide in PBS was added to Alhydrogel (two percent aqueous aluminum hydroxide gel, Sargeant, Inc., Clifton, NJ) to reach concentrations of 100 μg Aβ~~peptide per 1 mg of alum~~ peptide per 2 mg of alum. 10X PBS was added to a final dose volume of 200 ml in 1X PBS. The suspension was then gently mixed for approximately 4 hr at RT prior to injection.

Please replace the paragraph beginning at page 77, line 3, with the following amended paragraph:

To prepare formulation doses with Freund's Adjuvant (Group 4), 100 g of AN1792 in 200 μl PBS was emulsified 1:1 (vol:vol) with Complete Freund's Adjuvant (CFA) in a final volume of 400 μl for the first immunization. For subsequent immunizations, the antigen was similarly emulsified with Incomplete Freund's Adjuvant (IFA). For the formulations containing the adjuvants alum, MPL or QS21, 100 g per dose of AN1792 or AN1528 was combined with alum ~~(1 mg per dose)~~ (2 mg per dose) or MPL (50 g per dose) or QS21 (25 g per dose) in a final volume of 200 μl PBS and delivered by subcutaneous inoculation on the back between the shoulder blades. For the group receiving FA, 100 g of AN1792 was emulsified 1:1 (vol:vol) with Complete Freund's adjuvant (CFA) in a final volume of 400 μl and delivered intraperitoneally for the first immunization, followed by a boost of the same amount of immunogen in Incomplete Freund's adjuvant (IFA) for the subsequent five doses. For the group receiving AN1792 without adjuvant, 10 g AN1792 was combined with 5 g thimerosal in a final volume of 50 μl PBS and delivered subcutaneously. The ninth, control group received only 200 μl PBS delivered subcutaneously. Immunizations were given on a biweekly schedule for the first three doses, then on a monthly schedule thereafter on days 0, 16, 28, 56, 85 and 112. Animals were bled six to seven days following each immunization starting after the second dose for the measurement of antibody titers. Animals were euthanized approximately one week after the final dose. Outcomes were measured by ELISA assay of Aβ and APP levels in brain and by immunohistochemical evaluation of the presence of amyloid plaques in brain sections. In addition, Aβ-specific antibody titers, and Aβ-dependent proliferative and cytokine responses were determined.

Please replace the paragraph beginning at page 80, line 1, with the following amended paragraph:

The results of AN1792 or AN1592 treatment with various adjuvants, or thimerosal on cortical amyloid burden in 12-month old mice determined by ELISA are ~~shown in Fig. 15~~shown in Figs 15A-15E. In PBS control PDAPP mice the median level of total Aβ in the cortex at 12 months was 1,817 ng/g (Fig. 15A). Notably reduced levels of Aβ were observed in mice treated with AN1792 plus CFA/IFA (Fig 15C), AN1792 plus alum (Fig 15D), AN1792 plus MPL (Fig 15E) and QS21 plus AN1792 (Fig 15E). The reduction reached statistical significance ($p<0.05$) only for AN1792 plus CFA/IFA (Fig 15C). However, as shown in Examples I and III, the effects of immunization in reducing Aβ levels become substantially greater in 15 month and 18 month old mice. Thus, it is expected that at least the AN1792 plus alum, AN1792 plus MPL and AN1792 plus QS21 compositions will achieve statistical significance in treatment of older mice. By contrast, the AN1792 plus the preservative thimerosal (Fig 15D) showed a median level of Aβ about the same as that in the PBS treated mice. Similar results were obtained when cortical levels of Aβ42 were compared. The median level of A42 in PBS controls was 1624 ng/g. Notably reduced median levels of 403, 1149, 620 and 714 were observed in the mice treated with AN1792 plus CFA/IFA, AN1792 plus alum, AN1792 plus MPL and AN1792 plus QS21 respectively, with the reduction achieving statistical significance ($p=0.05$) for the AN1792 CFA/IFAβ treatment group. The median level in the AN1792 thimerosal treated mice was 1619 ng/g Aβ42.

Please replace the paragraph beginning on page 83, line 14 with the following replacement paragraph:

Sixty male and female, heterozygous PDAPP transgenic mice, 8.5 to 10.5 months of age were obtained from Charles River Laboratory. The mice were sorted into six groups to be treated with various antibodies directed to Aβ. Animals were distributed to match the gender, age, parentage and source of the animals within the groups as closely as possible. As shown in Table 10, the antibodies included four murine Aβ-specific monoclonal antibodies, 2H3 (directed to Aβ residues 1-12), 10D5 (directed to Aβ residues 1-16) (details of the deposit of 10D5 are discussed in Example VI, *supra*), 266 (directed to Aβ residues 13-28 and binds to monomeric but not to aggregated AN1792), 21F12 (directed to Aβ residues 33-42). A fifth group was treated with an Aβ-specific polyclonal antibody fraction (raised by immunization with aggregated AN1792). The negative control group received the diluent, PBS, alone without antibody.

Please replace the paragraph beginning on page 107, line 26 with the following replacement paragraph:

The brain homogenates were diluted 1:10 with ice cold Casein Diluent (0.25% casein, PBS, 0.05% sodium azide, 20 μg/ml aprotinin, 5 mM EDTA pH 8.0, 10 μg/ml leupeptin) and then centrifuged at 16,000 x g for 20 min at 4 C. The synthetic Aβ protein standards (1-42 amino acids) and the APP standards were prepared to include 0.5 M guanidine and 0.1% bovine serum albumin (BSA) in the final composition. The "total" Aβ sandwich ELISA utilizes monoclonal antibody (mAb) 266, specific for amino acids 13-28 of Aβ (Seubert, et al.), as the capture antibody, and biotinylated mAb 3D6, specific for amino acids 1-5 of Aβ (Johnson-Wood, et al), as the reporter antibody. The 3D6 mAb does not recognize secreted APP or full-length APP, but detects only Aβ species with an amino-terminal aspartic acid. The cell line producing the antibody 3D6 has the ATCC accession number PTA-5130, having been deposited on April 8, 2003. This assay has a lower limit of sensitivity of ~50 ng/ml (11 nM) and shows no cross-reactivity to the endogenous murine Aβ protein at concentrations up to 1 ng/ml (Johnson-Wood et al., *supra*).

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings of claims in the application:

Listing of Claims:

1. (Amended) A method of [preventing] prophylactically or therapeutically treating [an amyloidogenic] a disease associated with amyloid deposits of Aβ in the brain of a patient, comprising administering to the patient an effective dosage of [an] a pharmaceutical composition comprising a human, humanized or chimeric antibody that [binds to a component of an amyloid deposit in the patient] specifically binds to an epitope within Aβ1-7, and thereby prophylactically or therapeutically treating the patient [wherein the isotype of the antibody is human IgG1].

2. (Original) The method of claim 1, wherein the disease is characterized by cognitive impairment.

3. (Original) The method of claim 1, wherein the disease is Alzheimer's disease.

4. (Original) The method of claim 1, wherein the disease is Down's syndrome.

5. (Original) The method of claim 1, wherein the disease is mild cognitive impairment.

6. (Original) The method claim 1, wherein the antibody is of human isotype IgG1.

7. (Original) The method of any of the preceding claims, wherein the patient is human.

8. (Original) The method of claim 1, wherein the antibody specifically binds to an epitope within residues 1-6 of Aβ.

9. (Original) The method of claim 1, wherein the antibody specifically binds to an epitope within residues 1-5 of Aβ.

10. Cancel

11. (Original) The method of claim 1, wherein the antibody specifically binds to an epitope within residues 3-7 of Aβ.

12. (Original) The method of claim 1, wherein the antibody specifically binds to an epitope within residues 1-3 of Aβ.

13. (Original) The method claim 1, wherein the antibody specifically binds to an epitope within residues 1-4 of Aβ.

14. (Original) The method of claim 1, wherein after administration the antibody binds to an amyloid deposit in the patient and induces a clearing response against the amyloid deposit.

15. (Original) The method of claim 14, wherein the clearing response is an Fc receptor mediated phagocytosis response.

16. (Original) The method of claim 15, further comprising monitoring the clearing response.

17. (Original) The method of claim 1, wherein the antibody specifically binds to an epitope comprising a free N-terminal residue of Aβ.

18. (Amended) The method of claim 1, wherein the antibody binds to an epitope within residues of ~~1-10 of Aβ~~ 1-7 of Aβ wherein residue 1 and/or residue 7 of Aβ is iso-aspartic acid.

19. (Original) The method of claim 1, wherein the patient is asymptomatic.

20. (Original) The method of claim 1, wherein the patient is under 50.

21. (Original) The method of claim 1, wherein the patient has inherited risk factors indicating susceptibility to Alzheimer's disease.

22. (Original) The method of claim 1, wherein the patient has no known risk factors for Alzheimer's disease.

23. (Original) The method of claim 1, wherein the antibody is a human antibody.

24. (Original) The method of claim 1, wherein the antibody is a humanized antibody.

25. (Original) The method of claim 1, wherein the antibody is a chimeric antibody.

26. Cancel

27. (Original) The method of claim 1, wherein the antibody is a polyclonal antibody.

28. (Original) The method of claim 1, wherein the antibody is a monoclonal antibody.

29. (Original) The method of claim 1, further comprising administering an effective dosage of at least one other antibody that binds to a different epitope of Aβ.

30. (Original) The method of claim 1, wherein the isotype of the antibody is IgG1 or IgG4.

31. (Original) The method of claim 1, wherein the isotype of the antibody is IgG2 or IgG3.

32. (Original) The method of claim 1, wherein the antibody comprises two copies of the same pair of light and heavy chains.

33. (Original) The method of claim 1, wherein the antibody is a bispecific antibody comprising a first light and heavy chain pair that specifically binds to the epitope of Aβ and a second light and heavy chain pair that specifically binds to an Fc receptor on microglial cells.

34. (Original) The method of claim 1, wherein a chain of the antibody is fused to a heterologous polypeptide.

35. (Original) The method of claim 1, wherein the dosage of antibody is at least 1 mg/kg body weight of the patient.

36. (Original) The method of claim 1, wherein the dosage of antibody is at least 10 mg/kg body weight of the patient.

37. (Amended) The method of claim 1, wherein the antibody is administered with a carrier ~~as a pharmaceutical composition~~.

38. (Original) The method of claims 1, wherein the antibody is a human antibody to Aβ prepared from B cells from a human immunized with an Aβ peptide.

39. (Original) The method of claim 38, wherein the human immunized with Aβ peptide is the patient.

40. (Original) The method of claim 1, wherein the antibody specifically binds to Aβ peptide without binding to full-length amyloid precursor protein (APP).

41. (Original) The method of claim 1, wherein the antibody is administered intraperitoneally, orally, subcutaneously, intranasally, intramuscularly, topically or intravenously.

42-43: Cancel

44. (Original) The method of claim 1, further comprising monitoring the patient for level of administered antibody in the blood of the patient.

45. (Amended) The method of claim 70 or 71~~any of the preceding claims~~, wherein the occasions occur ~~antibody is administered in multiple dosages~~ over a period of at least six months.

46. (Amended) The method of claim 1, wherein the pharmaceutical composition ~~antibody is administered as a~~is a sustained release composition.

47. (Withdrawn) A pharmaceutical composition comprising an antibody that specifically binds to within residues 1-10 of Aβ and a pharmaceutical carrier.

48. (Withdrawn) A method of screening an antibody for activity in treating a disease associated with amyloid deposits of Aβ in the brain of a patient, comprising

contacting the antibody with a polypeptide comprising at least five contiguous amino acids of an N-terminal segment of A beginning at a residue between 1 and 3 of Aβ, the polypeptide being free of a C-terminal segment of Aβ,

and determining whether the antibody specifically binds to the polypeptide, specific binding providing an indication that the antibody has activity in treating Alzheimer's disease.

49. (Withdrawn) The method of claim 48, wherein the disease is Alzheimer's disease.

50. (Withdrawn) A method of screening an antibody for activity in clearing a biological entity physically associated with an antigen, comprising

combining the antigen-associated biological entity, the antibody and phagocytic cells bearing Fc receptors in a medium;

monitoring the amount of the antigen-associated biological entity remaining in the medium, a reduction in amount of the antigen-associated biological entity indicating the antibody has clearing activity against the antigen.

51. (Withdrawn) The method of claim 50, wherein the monitoring step monitors the amount of the antigen remaining in the medium.

52. (Withdrawn) The method of claim 50, wherein the combining comprises adding antigen-associated biological entity to the medium, and contacting the medium with the phagocytic cells bearing Fc receptors.

53. (Withdrawn) The method of any of claim 50, wherein the antigen-associated biological entity is provided as a tissue sample.

54. (Withdrawn) The method of claim 50, wherein the antigen is the biological entity.

55. (Withdrawn) The method of claim 50, wherein the tissue sample comprises an amyloid deposit.

56. (Withdrawn) The method of claim 55, wherein the tissue sample is from the brain of an Alzheimer's disease patient or a mammal animal having Alzheimer's pathology.

57. (Withdrawn) The method of claim 50, wherein the antigen is Aβ.

58. (Withdrawn) The method of claim 50, wherein the phagocytic cells are microglial cells.

59. (Withdrawn) The method of claim 50. wherein the tissue sample is selected from the group consisting of a cancerous tissue sample, a virally infected tissue sample, a tissue sample comprising inflammatory cells, a nonmalignant abnormal cell growth, and a tissue sample comprising an abnormal extracellular matrix.

60. (Withdrawn) A method of detecting an amyloid deposit in a patient, comprising administering to the patient an antibody that specifically binds to an epitope within amino acids 1-10 of Aβ and detecting the presence of the antibody in the brain of the patient.

61. (Withdrawn) The method of claim 60, wherein the antibody binds to an epitope within residues 4-10 of Aβ.

62. (Withdrawn) The method of claim 60, wherein the antibody binds to an epitope within residues 8-10 of Aβ.

63. (Withdrawn) The method of claim 60, wherein the antibody is labelled.

64. (Withdrawn) The method of claim 60, wherein the antibody is labelled with a paramagnetic label.

65. (Withdrawn) The method of claim 64, wherein the labelled antibody is detected by nuclear magnetic resonance.

66. (Withdrawn) The method of claim 64, wherein the antibody lacks capacity to induce a clearance response on binding to an amyloid deposit in the patient.

67. (Withdrawn) A diagnostic kit, comprising an antibody that specifically binds to an epitope with residues 1-10 of Aβ.

68. (Withdrawn) The kit of claim 67, further comprising labeling describing use of the antibody for in vivo diagnosis or monitoring of a disease associated with amyloid deposits of Aβ in the brain of a patient.

69. (New) The method of claim 1, wherein the method further comprises monitoring a response to the administration of the antibody in the patient.

70. (New) The method of claim 1, wherein a single dosage of the antibody is administered on multiple occasions.

71. (New) The method of claim 70, wherein the single dosage is administered once every week, once per every two weeks, once a month, once every 3 to 6 months, or yearly.

72. (New) The method of claim 70, wherein the multiple occasions occur at irregular intervals, and the method further comprises measuring blood levels of antibodies to Aβ to determine the intervals.

73. (New) The method of claim 70, further comprising administering a further dosage of antibody when the level of the antibody has declined below a predetermined percentage of a peak less baseline or a reference level of the antibody in the patient.

74. (New) The method of claim 1, further comprising administering a further dosage of antibody when the level of the antibody has declined below a reference level of the antibody in the patient.

75. (New) The method of claim 1, wherein the patient has the disease.

Amendments to the Drawings:

The first attached replacement drawing sheet (Figs. 1 and 2) has been amended to conform to 37 C.F.R. 1.84(l) standards for the character of lines, numbers and letters.

The second attached replacement drawing sheet (Figs. 3 and 4) has been amended to conform to 37 C.F.R. 1.84(l) standards for the character of lines, numbers and letters. Figure 4 has been further amended to replace "retrospelenial" with "retrosplenial."

The third attached replacement drawing sheet (Figs. 5 and 6) has been amended to conform to 37 C.F.R. 1.84(l) standards for the character of lines, numbers and letters.

The fourth attached replacement drawing sheet (Figs. 7 and 8) has been amended to conform to 37 C.F.R. 1.84(l) standards for the character of lines, numbers and letters.

The fifth attached replacement drawing sheet (Fig. 9) has been amended to replace "retroslpenial" with "retrosplenial."

The sixth attached replacement drawing sheet (Fig. 10) has been amended identify the upper and lower panels of Figure 10 as Figure 10A and 10B, respectively. Figure 10 has also been amended to replace "retroslpenial" with "retrosplenial."

The seventh attached replacement drawing sheet (Figs 11 and 12) includes Fig. 11 which has been amended to include a legend.

The eighth attached replacement drawing sheet (Figs. 13 and 14) has been amended to conform to 37 C.F.R. 1.84(l) standards for the character of lines, numbers and letters.

The ninth attached replacement drawing sheet (Fig. 15A) has been amended to correct an obvious error, *i.e.*, "p Malue" has been replaced with "p Value." Support this amendment is provided by the informal Figure 15 as originally filed in U.S. Application No.

09/201,430, filed November 30, 1998, which is incorporated by reference into the instant application.

The tenth attached replacement drawing sheet (Fig. 15B) has been amended to correct an obvious error, *i.e.*, "p Malue" has been replaced with "p Value." Support this amendment is provided by the informal Figure 15 as originally filed in U.S. Application No. 09/201,430, filed November 30, 1998, which is incorporated by reference into the instant application.

The eleventh attached replacement drawing sheet (Fig. 15C) has been amended to correct an obvious error, *i.e.*, "p Malue" has been replaced with "p Value." Support this amendment is provided by the informal Figure 15 as originally filed in U.S. Application No. 09/201,430, filed November 30, 1998, which is incorporated by reference into the instant application.

The twelfth attached replacement drawing sheet (Fig. 15D) has been amended to correct an obvious error, *i.e.*, "p Malue" has been replaced with "p Value." Figure 15D has been further amended to replace "2μg/ml alum" with "2 mg/ml alum." Support for these amendments is provided by the informal Figure 15 as originally filed in U.S. Application No. 09/201,430, filed November 30, 1998, which is incorporated by reference into the instant application.

The thirteenth attached replacement drawing sheet (Fig. 15E) has been amended to correct an obvious error, *i.e.*, "p Malue" has been replaced with "p Value." Support this amendment is provided by the informal Figure 15 as originally filed in U.S. Application No. 09/201,430, filed November 30, 1998, which is incorporated by reference into the instant application.

The fourteenth attached replacement drawing sheet (Fig. 16) has been amended to orient the words in a left-to-right fashion when the page is turned so that the top becomes the left side. Figure 16 has been further amended to replace "Anti AB" with "Anti-Abeta." Support for this amendment can be found on page 92, lines 25-33 of the specification.

The fifteenth replacement drawing sheet (Fig. 17) has been amended to orient the words in a left-to-right fashion when the page is turned so that the top becomes the left side.

The sixteenth attached replacement drawing sheet (Fig. 18) has been amended to orient the words in a left-to-right fashion when the page is turned so that the top becomes the left side.

The seventeenth attached replacement drawing sheet (Fig. 19) been amended to delete one of the two occurrences of the sequence "VGSNKGAIIG."

The eighteenth attached replacement drawing sheet (Fig. 20) been amended to delete one of the two occurrences of the sequence "VGSNKGAIIG."

Attachment: 18 Replacement Drawing Sheets

REMARKS/ARGUMENTS

After entry of this amendment claims 1-9, 11-25, 27-41, and 44-75 are pending and claims 1-9, 11-25, 27-41, 44-46, and 69-75 are under currently under examination. Claims 42-43 and 47-68 have been withdrawn from consideration and claims 42 and 43 have been subsequently canceled. Claims 10 and 26 have been canceled and new claims 69-75 have been added.

Claim 1 has been amended to incorporate the element from previous claim 10 (*i.e.*, antibody binds to an epitope within residues 1-7 of Aβ). The claim has also been amended to recite "prophylactically or therapeutically treating" instead of "preventing or treating". Support is provided at *e.g.*, p. 36, lines 14-23. The end of the body of the claim has also been amended to conform to the preamble. Claim 18 has been amended to delete "an epitope within residues 1-10 of Aβ" and to recite "an epitope within residues 1-7 of Aβ". Support is provided at *e.g.*, p. 15, lines21-22 and p. 18, lines 28-29. Claims 37 and 46 have been amended to more clearly state the invention. Claim 45 has been amended to depend from claim 70 or 71. No amendment should be viewed as acquiescence in any ground of rejection.

New claims 69-75 have been added. Support for the new claims is provided, *e.g.*, as follows: claim 69, p. 42, lines 24-31; claim 70, p. 37, line 28; claim 71, p. 37, lines 24-25 and 28-29; claim 72, p. 37, lines 29-30; claim 73, p. 45, lines 9-20; claim 74, p. 42, lines 24-31 and p. 45, lines 1-20; and, claim 75, p. 36, line 21.

The specification has been amended to (1) delete the priority claim under 35 U.S.C. § 120; (2) conform with the replacement drawing sheets submitted herewith; (4) correct obvious errors; and, (3) identify two cell lines producing the 10D5 and 3D6 antibodies, respectively, deposited with the ATTC. Thus, the amendments to the specification contain no new matter.

The specification has been amended to conform with the replacement sheets submitted herewith. The paragraphs beginning on page 7, line 12 and p. 59, line 25 describe Figure 10; and to conform with the amendment to Figure 10; both paragraphs have been amended to identify the upper and lower panels of Figure 10 as Figure 10A and 10B,

respectively. The paragraph beginning on page 7, line 27 of the specification describes Figure 15. The paragraph has been replaced with six replacement paragraphs, which describe Figures 15A-15E, 15A, 15B, 15C, 15D, and 15E, respectively. The paragraphs beginning on p. 7, line 32 and p. 8, line 5 describe Figures 19 and 20, respectively; and, to conform with the amendment to Figures 19 and 20 have been amended to delete "The results for peptide sequence VGSNKGAIIG (SEQ ID NO:32) are shown twice." The paragraphs beginning on page 76, line 17, and page 77, line 3, have been amended to conform the alum concentration to the alum concentration recited in Figure 15 as filed in Application No. 09/201,430, filed November 30, 1998, which is incorporated herein by reference. The paragraph beginning on page 80, line 1 has been amended to identify Figures 15A-15E.

The specification has been amended to correct obvious errors. The paragraphs beginning on p. 16, line 16 and p. 62, line 12 have been amended to replace the plain text font of genus and species names with an italicized font, *e.g.*, "Salmonella" has been replaced with "*Salmonella.*" The paragraph beginning on page 46, line 19 has been amended to correct an obvious error, *i.e.*, "that binds to A to the patient" has been amended to recite, "that binds to Aβ in the patient" and "of Aβdo not" has been amended to recite "of Aβ do not show."

Applicants deposited the cell line producing the antibody 10D5 and the cell line producing the antibody 3D6 with the ATCC on April 8, 2003. Applicants submit a statement under MPEP § 2406.02 herewith. The cell lines deposited with the ATCC are the cell lines producing the antibodies 10D5 and 3D6, respectively, which are identified in the instant specification and in Application No. 09/580,518, filed May 26, 2000. Applicants have amended the paragraphs beginning on p. 68, line 17, p. 83, line 14, and p. 107, line 26 of the specification to recite the depository, accession number, and deposit date of the cell lines producing the 10D5 and 3D6 antibodies, respectively. These amendments do not add new matter (*see In re Lundak*, 227 USPQ 90 (Fed. Cir. 1985) and MPEP § 2406.01).

Election/Restriction

Withdrawal of the species election as between epitopes within residues 1-3, 1-4, 1-5, 1-6, 1-7 or 3-7 of Aβ is acknowledged.

Sequence Requirements

The Office Action takes the position that the instant application fails to comply with 37 C.F.R. §§ 1.821-1.825 because Figures 19 and 20 disclose an amino acid sequence without an appropriate SEQ ID NO. (Applicants respectfully point out that this issue was addressed in Paper No. 25, filed February 18, 2003.) As discussed in the Amendments to the Drawings section, Figures 19 and 20 have been amended to delete one of the two occurrences of the sequence "VGSNKGAIIG". As discussed above, the specification has been amended to conform to the replacement drawing sheet showing Figure 19 and the replacement drawing sheet showing Figure 20.

Drawings

Amendments to Figure 10

Figure 10 was objected to because the upper and lower panels were unlabeled. The replacement Figure 10 drawing sheet, attached hereto, has been amended to identify the top panel as "10A" and the bottom panel as "10B." The specification has been amended to conform to the replacement Figure 10 drawing sheet.

Amendments to Figure 11

Figure 11 was objected to because it lacked an appropriate legend. Figure 11 has been amended to include a legend which indicates the treatment group. Support for the amendment to Figure 11 is found at, *e.g.*, p. 7, lines 14-15; and, p. 62, line 23 to p. 63, line 11.

Information Disclosure Statement

The references cited by the information disclosure statements filed November 3, 2000 (Paper No. 4), January 8, 2001 (Paper No. 6), and February 18, 2003 (Paper No. 18) include all the elements required to comply with 37 C.F.R. §§ 1.97-98 that are known to Applicants.

Double Patenting

Statutory Double Patenting

U.S. Application No. 09/322,289

Claims 1-41 and 44-47 are provisionally rejected for same invention double patenting over claims 1-2, 4-8, and 10-24 of copending U.S. Application No. 09/322,289. Applicants note rejection of claims 10 and 26 is moot in light of their cancellation. Applicants request this issue be held in abeyance until indication of otherwise allowable subject matter. It is likely that the claims in the cited case will differ from those pending in the current case at the time of allowance of the present case. However, if claims from the different case are in conflict at that time, applicants will amend the claims in the cited case to avoid the conflict.

U.S. Application No. 09/580,015

Claims 1-41 and 44-47 are provisionally rejected for same invention double patenting over claims 1-46 of copending U.S. Application No. 09/580,015. Applicants note rejection of claims 10 and 26 is moot in light of their cancellation. Applicants request this issue be held in abeyance until indication of otherwise allowable subject matter. It is likely that the claims in the cited case will differ from those pending in the current case at the time of allowance of the present case. However, if claims from the different case are in conflict at that time, applicants will amend the claims in the cited case to avoid the conflict.

U.S. Application No. 09/724,273

Claims 1-12, 14-15, 19-23, and 26 are provisionally rejected for same invention double patenting over claims 1-41 of copending U.S. Application No. 09/724,273. In response to the restriction requirement mailed on July 2, 2002 for 09/724,273, Applicants elected Group VI, claims 60-66 which are drawn to a method of detection. Subsequently, claims 1-59 and 67-68 have been canceled (*see* Paper 23, filed July 21, 2003). Based on the foregoing, applicants requested the rejection be withdrawn.

Claims Rejections Under Non-Statutory Double Patenting

U.S. Application No. 09/497,553

Claims 1-41 and 44-47 stand provisionally rejected for obviousness type double patenting over claims 42 and 43 of U.S. Application No. 09/497,533. Applicants note rejection of claims 10 and 26 is moot in light of their cancellation. Applicants propose this issue be held in abeyance until indication of allowability in the present case. Applicants will then consider providing a terminal disclaimer over cited cases provided the cited case has been or is about to patented, the claims in the cited case have not been divided from those in the present case by restriction requirement or election of species, and the claims in the cited case are in conflict with those in the present case at this time.

U.S. Application No. 09/724,495

Claims 1-41 and 44-47 stand provisionally rejected for obviousness type double patenting over claims 1-24, 28-32 and 36-37 of U.S. Application No. 09/724,495. Applicants propose this issue be held in abeyance until indication of allowability in the present case. Applicants will then consider providing a terminal disclaimer over cited cases provided the cited case has been or is about to patented, the claims in the cited case have not been divided from those in the present case by restriction requirement or election of species, and the claims in the cited case are in conflict with those in the present case at this time.

U.S. Application No. 09/979,701

Claims 1-41 and 44-47 stand provisionally rejected for obviousness type double patenting over claims 1-47 Application No. 09/979,701. Applicants propose this issue be held in abeyance until indication of allowability in the present case. Applicants will then consider providing a terminal disclaimer over cited cases provided the cited case has been or is about to patented, the claims in the cited case have not been divided from those in the present case by restriction requirement or election of species, and the claims in the cited case are in conflict with those in the present case at this time.

U.S. Application No. 09/724,961

Claims 1-41 and 44-47 stand provisionally rejected for obviousness type double patenting over claims 1-12, 14-15, 19, 23, and 26 of copending Application No. 09/724,961. Applicants propose this issue be held in abeyance until indication of allowability in the present case. Applicants will then consider providing a terminal disclaimer over cited cases provided the cited case has been or is about to patented, the claims in the cited case have not been divided from those in the present case by restriction requirement or election of species, and the claims in the cited case are in conflict with those in the present case at this time.

Claim Rejections

Rejection of Claims 1-41 and 44-47 Under 35 U.S.C. § 112, First Paragraph

¶14. The Examiner says the above claims are enabled for treating Alzheimer's disease via administration of an antibody that specifically binds to an epitope within residues 1-3, 1-4, 1-5, 1-6, 1-7 or 3-7 of Aβ. However, the Examiner alleges the claims are not enabled for preventing Alzheimer's disease, preventing or treating Down's syndrome or administration of an antibody that binds other components of an amyloid deposit. Due to the length of the rejection, applicants address the Examiner's comments by paragraph using the numbering of the office action.

¶15. The Examiner summarizes the subject matter of the claims. No response is needed.

¶16. The Examiner cites Schenk, Games and Chen as teaching mice that exhibit Alzheimer's-type over-production and build up of anti-Aβ amyloid within the brain. However, the Examiner alleges that it is recognized in the art that these mice do not exhibit Down's syndrome or other amyloidogenic diseases. The Examiner also cites Munch as evidencing lack of correlation between beneficial effects in mice and humans.

The claims have been amended to refer to diseases having amyloid deposits of Aβ in the brain of the patient. Such diseases include Alzheimer's disease, Down's Syndrome, and mild cognitive impairment (*see* the specification at p. 2, lines 27-29 and p. 12, line 27 to p. 13,

line 3). Both of the latter two diseases are characterized at least in part by similar pathology to Alzheimer's disease and often progress to Alzheimer's disease (*see e.g.*, Hyman, *Prog. Clin. Biol. Res.*, 379, 123-42 (1992); Brugge *et al.*, *Neurology*, 44, 232-8 (1994); and, Winblad, *Acta Neurol. Scand. Suppl.*, 179, 83-93 (2003), all attached hereto). In the case of Down's syndrome, the similarity in pathology with Alzheimer's disease can be explained by the trisomy of chromosome 21 on which the gene encoding amyloid precursor protein resides. Extra production of this protein due to the extra copy of the gene can lead to extra production of its proteolytic processing product Aβ and hence deposition in to plaques (*see* Hyman). Because Alzheimer's disease, Down's syndrome and mild cognitive impairment are characterized by similar pathology (*i.e.*, amyloid deposits of Aβ) in the same organ (*i.e.*, the brain), the skilled person has reason is reason to expect that a treatment that is effective against Alzheimer's disease is also effective against the other diseases.

Although the mice discussed in the Schenk, Games and Chen papers were created as a model of Alzheimer's disease, there is no reason to think, much less art recognition, that they are not useful as models for other diseases, such as Down's syndrome, which are characterized at least in part by essentially the same pathology as Alzheimer's disease. For a mouse to be useful as a model of a disease, it is not essential that the mouse model manifest every aspect of the pathology present in the disease. Rather, it is sufficient that the model manifest one aspect of pathology that contributes to the disease. In the case of Down's syndrome, there is every reason to expect that amyloid deposits of Aβ in the brain of a patient contribute to the disease as they do in Alzheimer's disease, and that treatment that reduces accumulation or inhibits further accumulation of these deposits in a Down's syndrome patient would be of benefit to the Down's patient as to the Alzheimer's patient. The claims as presently formulated do not require that the treatment completely eradicate or completely prevent the disease. Thus, it is immaterial that there may be some components of Down's syndrome that may not be amenable to treatment by the claimed methods. Rather, it is sufficient that the methods result in some benefit in Down's syndrome patients.

The Munch reference is not relevant to whether the methods are effective for Down's syndrome patients. The reference reports that a small number of patients experienced inflammatory side effects in a human clinical trial of Alzheimer's disease patients. However, the existence of side effects, assuming *arguendo* such exist, in a small number of patients is consistent with a successful treatment. Few approved drugs, particularly those for treating serious diseases, are entirely free of side effects. Indeed, it appears from ¶14 of the office action that the Examiner agrees that the reference is not detrimental to enablement of methods of treating Alzheimer's disease. The reference is no more detrimental to methods of treating Down's syndrome.

¶17. The Examiner alleges that the methods are not effective to prevent onset of disease. The Examiner alleges that all PDAPP mice exhibited plaques regardless of treatment regime. This rejection is moot in view of the amendment to the claims to recite prophylaxis or therapeutic treatment of disease. Prophylaxis is defined at *e.g.*, p. 36, lines 14-19 of the specification and does not require absolute prevention of the disease. In fact, the Examiner's allegation that all PDAPP mice exhibited plaques regardless of treatment is incorrect. When PDAPP mice were treated prophylactically before development of plaques (which starts at about six months), seven of nine mice had no detectable amyloid in the brains (*see* Example 1, particularly, p. 49, lines 9-10). Thus, prophylactic treatment can prevent development of plaques.

¶¶18-24.

The Examiner cites several references to illustrate the art of Alzheimer's disease. Sigurdson is cited as teaching that human Aβ differs in sequence from its mouse counterpart, from which the Examiner alleges that an autoimmune response may develop in humans that is not present in the PDAPP mouse. The Examiner also cites Sigurdson as teaching that administration of Aβ leads to cerebral inflammation and may seed fibril or amyloid formation. Su is cited as teaching that rats administered with human Aβ1-40 develop damage to the blood brain barrier, activated microglial and focal pulmonary hemorrhages. Munch is cited as discussing inflammatory side effects in humans administered Aβ42. Furlan is cited as discussing

autoimmune encephalomyelitis in C57/BL6 mice administered Aβ42. Spooner is cited as teaching that the route of administration, regime of administration, and genetic background of mice administered Aβ may affect antibody response. Monsonego is cited as teaching the immune responses from Aβ immunization of transgenic mice may taper of after a succession of administrations.

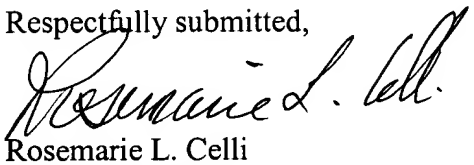
All of the references cited by the Examiner are directed to active immunization with Aβ. In contrast, the present claims are directed to passive administration of antibodies rather than active immunization with Aβ. It is not seen how the issues of side effects or generation of antibodies resulting from active immunization discussed in the cited references (which applicants do not concede in any event) are relevant to passive immunization as claimed. Further, the issue of potential side effects is not necessarily detrimental to enablement as discussed above in ¶16.

¶25. The Examiner alleges that the specification fails to provide guidance for the broad range of diseases encompassed by the claims. The Examiner alleges that undue experimentation would be required in de novo determination of formulations with acceptable toxicity and immunogenicity that are successfully delivered to target sites in appropriate cells and/or tissues.

As noted previously, the amended claims are directed to diseases associated with amyloid deposits of Aβ in the brain of a patient. It is reasonable to expect that if antibodies binding to an epitope with Aβ1-7 reduce or inhibit further accumulation of these deposits in Alzheimer's patient's, they would do likewise when administered in the same or similar regime in other diseases where the same pathology is present in the same target tissue. Any toxicity of the antibodies would be the same regardless of the disease treated. Likewise, the target tissue would be the same, *i.e.*, the brain, in all diseases included by the amended claims. Thus, no additional experimentation is required to investigate toxicity or delivery to a new target tissue. Therefore, it is submitted that the Examiner has not met his burden of proving that the claimed methods would not be expected to be effective for diseases associated with amyloid deposits of Aβ in the brain besides Alzheimer's disease.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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